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REGIOSPECIFIC MONOALKYLATION OF UNSATURATED IMINES DERIVED FROM CROTONALDEHYDE

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Recently, we had to alkylate selectively crotonaldehyde at the alpha position. During the course of working on this problem, alkylation reactions of this type were reported on the free aldehyde[1] and on its *t*-butylimine derivative.[2] However, these

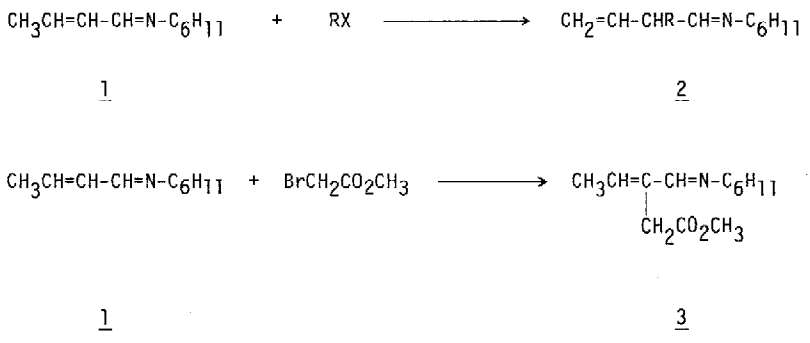
$$CH_3CH{=}CH{-}CHO \;+\; RX \longrightarrow CH_3CH{=}CR{-}CHO \;+\; R'X \longrightarrow CH_2{=}CH{-}CR'R{-}CHO$$

reactions suffered from low to modest yields, lack of regiospecificity, considerable dialkylation, and non-ideal stoichiometry, problems which clearly limit synthetic utility. We wish to describe a high yield and regiospecific method of monoalkylating crotonaldehyde imines which utilizes nearly ideal stoichiometry.

The cyclohexylimine of crotonaldehyde, 1, was used for these alkylation reactions. This material was conveniently prepared by adding (30 min) a solution of crotonaldehyde (1 equiv) 10 M in benzene to a chilled (-15°) mixture of cyclohexylamine (2.1 equiv) containing potassium carbonate (0.3 equiv). After addition was complete, the reaction was warmed to 0° for 1 hr and then to 22° for 3.5 hrs. Distillation of the reaction

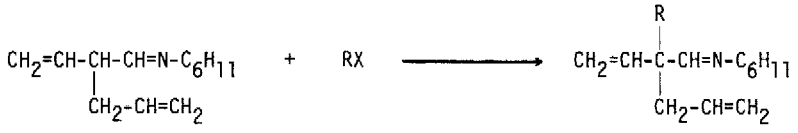
mixture at 0.3 torr (pot temperature 120°) gave a major fraction (bp 37°) which on redistillation at 3 torr gave pure 1 (bp 75°) in 82% yield.[3]

Monoalkylation at the alpha position of 1 can be realized in the following manner. Imine 1 (1 equiv) was added neat at 0° to a solution of lithium diisopropylamide (1 equiv, 0.5 M in THF) containing hexamethyl phosphoramide (1 equiv). The resulting bright yellow solution was stirred for 10 min at 0° then cooled to -78°. After stirring for an additional 30 min, the alkylating agent (1.07 equiv) was added. Under these conditions, the products formed are represented by the structure 2 where R is the residue introduced by alkylation with the following halides: methyl iodide (yield 98%, reaction time 4.5 hrs), allyl bromide (100%, 4.5 hrs), propargyl bromide (95%, 3.5 hrs), 1-bromo-3-chloro-2-butene (95%, 2 hrs), benzyl bromide (100%, 4 hrs), *iso*-propyl iodide (95%, 20 hrs), and *n*-butyl iodide (95%, 4.5 hrs).[4] The only exception to these results was encountered with methyl bromoacetate (1.07 equiv) which gave on alkylation at -78° for 4.5 hrs a quantitative yield of compound 3.[5]



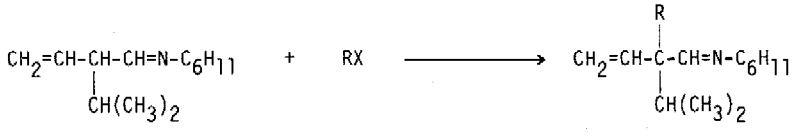
A second alkylation reaction leading to imines with a quaternary alpha carbon atom is also possible. These reactions have been carried out on imines 4 and 5 using

the same experimental conditions already described for the alkylation of compound 1. Imine 4 gave rise to products represented by the formula 6 utilizing the following halides: methyl iodide (yield 86%, reaction time 12 hrs), allyl bromide (99%, 2.5 hrs), 1-bromo-3-chloro-2-butene (95%, 3 hrs), benzyl bromide (100%, 3 hrs), *iso*-propyl iodide (91%, 10 hrs), and *n*-butyl iodide (92%, 48 hrs). Reaction of 4 with methyl bromoacetate (3 hrs, -78°) gave an 80% yield of alpha C-alkylation accompanied by 20% N-alkylation.



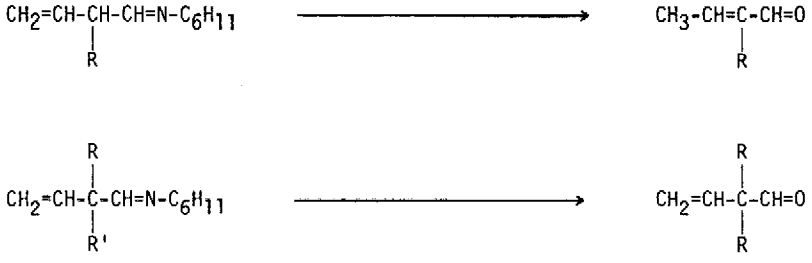
4 6

Alkylation of compound 5 afforded products represented by the structure 7 using the following halides: methyl iodide (yield 98%, reaction time 5.5 hrs), allyl bromide (97%, 5.5 hrs), 1-bromo-3-chloro-2-butene (100%,10 hrs), benzyl bromide (100%, 5.5 hrs), *iso*-propyl iodide (97%, 6 hrs)[6], and *n*-butyl iodide (92%, 8 hrs)[6]. Reaction of 5 with methyl iodoacetate gave a 95% yield of the N-alkylated product (-78°, 5.5 hrs).



5 7

All of these imines are easily hydrolyzed into the free aldehyde by stirring (1 hr) a 0.5 M solution of the imine dissolved in ether with an equal volume of a buffered (pH 4.5) aqueous acetic acid solution prepared from acetic acid (2.5 ml), water 2.5 ml) and sodium acetate (1.08 g). Ater standard work-up, the corresponding aldehydes were obtained in yields ranging from 85% to 96%.



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REFERENCES

1. S. A. G. de Graff, P. E. R. Oosterhoff, and A. van der Gen, *Tetrahedron Letts.*, 1653 (1974).

2. K. Takabe, H. Fujiwara, T. Katagiri, and J. Tanaka, *ibid.*, 1237 (1975).

3. Satisfactory physical data were obtained for all new compounds.

4. All alkylation reactions were carried out at -78° and the reaction mixtures quenched at -78° with saturated ammonium chloride. Products are conveniently isolated by distillation. The regiospecificity for each alkylation was determined by nmr, mass spec, and GC analysis. Contamination by other isomers (gamma-carbon alkylation, dialkylation, or nitrogen alkylation) was less than 1.5% in all cases except where specifically noted in the text.

5. Methyl iodoacetate also gives the same result.

6. Two equivalents of hexamethyl phosphoramide were used for this reaction.